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EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,799	JOHANSEN, JACK T	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment of claims 1 and 28 in the paper filed on 11/24/2008 is acknowledged.

Claims 1-28 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 103(a)

2. The rejection of claims 3-5 and 24 under 35 U.S.C. 103(a) as being unpatentable over Berglund et al., and further in view of Bambara et al. (1975, previously cited) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

Rejections that are Maintained

Claim Rejections Maintained - 35 USC § 102

3. The rejection of claims 1, 2, 6-8, 10-14, 16-21, 25, and 28 under 35 U.S.C. 102(b) as being anticipated by Berglund et al. (United States Patent 6,090,288 issued July 18, 2000) is maintained. Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that Berglund et al. teach purification of oligonucleotides using an increasing pH gradient together with a substantial increase in metal salt

concentration. However while Berglund et al. may teach this, Berglund et al. also teach purification of oligonucleotides using an increasing pH gradient without a substantial increase in metal concentration and thus anticipate the instant claims. Berglund et al. teach this as follows.

First, Berglund et al. teach that oligonucleotides can be purified by just increasing of pH (see claim 14 step c). In claim 14, Berglund teaches that elution can be accomplished by any one of three elements alone and by any combination of those three elements by teaching these elements as "and/or" elements. As one of the elements is elution by salt, Bergund et al. specifically teach that that element need not change, that is, that elution can be accomplished just by increasing of pH alone. Thus the teachings of Berglund anticipate instant claims 1 and 28 steps a and b and step d (an alternative to step c).

Second, Berglund et al. teach that the salt concentration can be decreased when a pH gradient is used (see column 2 lines 33-44), thus further meeting the limitations of instant claims 1 and 28, especially step d.

Thus as given in the prior Office action and her, Berglund et al. teach the claimed method and the rejection is maintained.

Rejections Necessitated by Amendment

New Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Berglund et al. (United States Patent 6,090,288 issued July 18, 2000).

Berglund et al. teach as noted above and in the prior Office action, mailed on 09/02/2008.

Regarding claim 5, Berglund et al. teach that the salt concentration can be decreased when a pH gradient is used (see column 2 lines 33-44) and thus does not substantially increase in salt concentration.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 3-5 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claim 1 above, and further in view of Bloch (United States Patent 5,856,192 issued January 5, 1999).

Berglund et al. teach as noted above.

Berglund et al. teach where the compositions comprise amines but do not specifically teach where the compositions comprise polyethyleneimine, potyimizadole, polyhistidine or polylysine.

Regarding claims 1-3 and 28, Bloch teaches methods of separating a target oligonucleotide from an impurity, in a mixture comprising said target oligonucleotide and said impurity, using a titratable anion exchange composition, (entire patent especially the Title and Abstract) comprising the steps:

a) binding said target oligonucleotide to said titratable anion exchange composition which can comprise polyethyleneimine (see claim 6) or which can comprise polylysine (see column 6 lines 63-66) in the presence of a solution having a first pH; and

b) passing a solution through said titratable anion exchange composition with target oligonucleotide bound thereon, wherein the pH of said elution solution is changed over time through a pH gradient (column 17 line 16) thereby to elute said target oligonucleotide, wherein said impurity elutes at a different pH than said target oligonucleotide and wherein

c) the elution solution is substantially free from metal salts such that subsequent desalting of the eluted oligonucleotide is not required by teaching

> "Solvents for salt-gradient anion-exchange separation of nucleic acids, especially double-stranded DNA and especially by liquid chromatography, are improved by replacing NaCl [a metal salt] as the eluting salt with any of a wide range of alkyl ammonium salts [non-metal salts] and can be used to elute nucleic acids in strict order of increasing length, with reduced sensitivity to elution temperature and salt concentration" (see 1st sentence of the Abstract);

Regarding claims 1 and 28, Bloch teaches pH gradients but does not specifically teach increasing the pH over time.

Regarding claim 4, Bloch teaches that elution is done without metal salts and thus necessarily is substantially free of metal salts (see 1st sentence of the Abstract).

Regarding claim 5, Bloch teaches that elution can be isocratic (column 17 line 15) and thus does not substantially increase in salt concentration over time

Berglund et al. teach separating oligonucleotides from impurities using a titratable anion composition comprising amines by increasing pH over time. Berglund et al. do not specifically teach where the amines are polyethyleneimine or polylysine. Bloch teaches separating oligonucleotides from impurities using a titratable anion composition comprising polyethyleneimine or polylysine by changing pH over time. Bloch does not specifically teach increasing the pH over time. Because both Berglund et al. and Bloch teach separation using amines, it would have been obvious to one skilled in the art to substitute the amines which are polyethyleneimine or polylysine as taught by Bloch for the amines taught by Berglund et al. in order to achieve the predictable result of a method of separating oligonucleotides from impurities using a titratable anion composition comprising amines which are polyethyleneimine or polylysine by increasing pH over time. Also, motivation to do so is provided by Bloch who teach that their: "Anion-exchange chromatography with these solvents [without metal salts] is well suited for identification of DNA fragments on the basis of size, with greater accuracy, precision, and resolvable size range than often is possible with gel electrophoresis" (see 2nd sentence of the Abstract). Furthermore, Bloch teaches that use of non metal salts,

which are di-, tri-, or tetra-alkylammonium cations in combination with a variety of anions, in solvents for chromatography (see column 8 lines 34-52) improves anion-exchange separation and analysis of nucleic acids (see column 9 lines 48-50). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

8. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claims 1 and 8 above, and further in view of Bloch (1999) and Crane et al. (1992, previously cited).

Berglund et al. teach as noted above.

Berglund et al. do not specifically teach polyethyleneimine-derivatized silica gel.

Regarding claim 9, Bloch teach polyethyleneimine (as given above) and that it can be attached covalently to a backbone of silica (see column 11 lines 32-40). Bloch does not specifically teach silica gel.

Regarding claim 9, Crane et al. teach polyethyleneimine-derivatized silica gel for affinity chromatography (entire reference, especially the Title).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the titatrable anion exchange composition of Berglund et al. by using polyethyleneimine-derivatized silica gel as suggested by Bloch and Crane et al. with a reasonable expectation of success. The motivation to do so is provided by Crane et al. who teach the usefulness of

polyethyleneimine-derivatized silica gel in chromatography and the teaching of Bloch who teach that polyethyleneimine-derivatized silica gives improved methods for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

9. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claims 1 and 7 above, and further in view of Asteriadis et al. (1976, previously cited).

Berglund et al. teach as noted above.

Berglund et al. do not specifically teach a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH.

Regarding claim 15, Asteriadis et al. teach a method using a solution of NH_4OH (see p. 67, 1st sentence).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Berglund et al. by using a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH as suggested by Asteriadis et al. with a reasonable expectation of success. The motivation to do so is provided by Asteriadis et al. who teach the usefulness of a method of low salt, a styrene-divinyl benzene copolymer, or a solution of NH_4OH for purification of oligonucleotides and the teaching of Berglund et al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

10. Claims 22, 23, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claim 1 above and further in view of Fruchtel et al. (1996).

Berglund et al. teach as noted above.

Berglund et al. teach a method wherein a target oligonucleotide is 5'-O-protected, is 5'-O-trityl protected, but do not specifically teach where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid.

Regarding claims 20 and 21, Fruchtel et al. where the target oligonucleotide is 5'-O-trityl protected (entire reference, especially p. 20 1st paragraph).

Regarding claims 22 and 23, Fruchtel et al. teach that acid condition cleave 5'-O-trityl protecting group including acetic acid (see 2nd sentence on page 20: " . . . the trityl anchoring bond can be cleaved by very weak acids such as acetic acid").

Regarding claim 26, Fruchtel et al. teach where the target oligonucleotide is is 5'-O-dimethoxy-trityl protected (entire reference, especially Scheme 41 on p 39 and footnote on page 17).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the teachings of Berglund et al. where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid; as suggested by Fruchtel et al. with a reasonable expectation of success. The motivation to do so is provided by Fruchtel et al. who teach the

usefulness of a target oligonucleotide which is 5'-O-protected, which is 5'-O-trityl protected, where there is a sufficient amount of an acidic solution to cleave said 5'-O-trityl protecting group from a target oligonucleotide prior to elution, and where acidic solution comprises aqueous acetic acid; and the teaching of Berglund et al. for the separation of oligonucleotides. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

11. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berglund et al. as applied to claim 1 above and further in view of Bambara et al. (1975, previously cited), Bloch (1999), Crane et al. (1992 previously cited), and Asteriadis et al. (1976 previously cited).

Berglund et al. teach as noted above.

Berglund et al. do not specifically teach a method wherein a titratable anion exchange composition comprises polyethyleneimine, polyimizadole, polyhistidine or polylysine conjugated to a synthetic polymer support; and the solutions comprises one or more specifically of NH_4HCO_3 and/or NH_4OH.

Regarding claim 27 in part that Bambara et al. teach a method wherein a solution increases from a pH of 7.5 which is about 8 to a pH of 8.5, which is about 11; teach solutions substantially free of metal salts where the change in buffer does not substantially increase salt concentration over time; teach an polyethyleneimine conjugated to solid support; and teach an amine carbonate.

Regarding claim 27 in part, Bloch teach polyethyleneimine (as given above) and that it can be attached covalently to a backbone of silica (see column 11 lines 32-40). Bloch does not specifically teach silica gel.

Regarding claim 27 in part, Crane et al. teach polyethyleneimine-derivatized silica gel for affinity chromatography (entire reference, especially the Title).

Regarding claim 27 in part, Asteriadis et al. teach a method wherein a solution is relatively of relatively low salt concentration, that is substantially free of metal salts and other salts (entire reference, especially p. 65, 2nd paragraph, 2nd sentence).

Regarding claim 27 in part, Asteriadis et al. teach a method using a solution of NH_4OH (see p. 67, 1st sentence).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Berglund et al. by using an amine which is polyethyleneimine conjugated to solid support as taught by Bambara et al.; by using a polyethyleneimine-derivatized silica gel as suggested by Bloch and Crane et al.; by using a solution of relatively low salt concentration, and a solution of NH_4OH as suggested by Crane et al. and Asteriadis et al. with a reasonable expectation of success. The motivation to do so is provided by Bloch who teaches improved chromatography using polyethyleneimine-derivatized silica and by Crane et al. and Asteriadis et al. who teach the usefulness of a polyethyleneimine-derivatized silica gel, a solution of relatively low salt concentration, and a solution of NH_4OH and the teaching of Bambara et al. for the separation of oligonucleotides with an amine which is polyethyleneimine can be achieved with a pH increase from pH 7.5 to pH 8.5. Thus, the

claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

12. No claim is free of the prior art.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
February 11, 2009

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637